The Addition of Ezetimibe to Statin therapy in Patients with Homozygous Familial Hypercholesterolaemia

Submitted in fulfilment with the requirements for the degree Master in Medicine (MMed)

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ABSTRACT

Background: Homozygous Familial hypercholesterolaemia (HoFH) is a rare genetic disorder affecting approximately one in every million people worldwide. It is characterized by severely elevated LDL-cholesterol (LDL-C) levels usually as a result of mutations in both LDL receptor alleles, and is associated with a markedly increased risk of premature cardiovascular disease with death often occurring in the first 3 decades of life. Standard treatment with statin therapy has been shown to yield suboptimal results with additional therapy required to achieve lower LDL-C levels. As not all centers worldwide have access to newer treatment modalities, cheaper and more accessible therapy needs to be considered. The addition of ezetimibe to statin therapy in HoFH individuals has only been reported in one previous study, but in that study other factors which may have influenced the response to ezetimibe such as body mass index (BMI), gender and the type of LDLR mutation were not evaluated

Objectives: Firstly to assess whether the addition of ezetimibe to statin therapy can result in further reduction in LDL-cholesterol in subjects with HoFH. Secondly, to assess whether the reduction in LDL-C (response rate) is dependent on the underlying LDLR mutations, gender and/or BMI. Lastly, to compare HoFH patients which showed higher responses in LDL-C reduction to ezetimibe (“responders”) to those who responded poorly (non-responders),

Study design: This was a retrospective study which evaluated HoFH patients known to the Charlotte Maxeke Johannesburg Academic Hospital’s lipid clinic. All patients were confirmed to have HoFH and were already on high intensity statin therapy prior

to initiating ezetimibe at a fixed dose of 10mg daily given orally. Their lipograms prior to ezetimibe initiation were recorded and used as a baseline. In addition, their BMI, gender, age, FH genotype and cardiovascular complications were recorded. Follow up lipograms were recorded at 3 and 6 month after ezetimibe initiation.

Results: 48 patients who fulfilled the entry criteria were eligible for the study. Of the 48 patients, 24 were males and 24 females. The average BMI in males was 22.7 ± 6.9 kg/m^2 and 24 ± 7.1 kg/m^2 in females. The two commonest FH genotypes were Afrikaner FH1/FH1 (17 patients) and Afrikaner FH1/FH2 (11 patients). Age ranged between 3 and 48 years with a mean age of 25 years. 65% of patients had documented coronary artery disease or aortic stenosis. 86% of patients were on high intensity statin therapy (atorvastatin 80mg or rosuvastatin 40 mg daily) prior to starting ezetimibe. Despite high intensity statin therapy, mean LDL-C at baseline was 12.1 ± 3.3 mmol/L, decreasing to 10 ± 3.4 mmol/L after 3 months of ezetimibe therapy, and 10.4 ± 3.3 mmol/L at 6 months (p=0.0018). The mean percentage reduction of LDL-C on ezetimibe was -18.9% after 3 months and -17.6% at 6 months. There was no significant change in HDL-C or triglyceride levels with the addition of ezetimibe, p>0.05. Response of LDL-C based on BMI, gender and LDLR mutation was evaluated at 3 months. Overweight patients had an overall better response compared to normal weight patients, with a mean percentage reduction of -20.5% vs -15.7% (p=0.02). A significant difference in response to ezetimibe was also seen amongst different FH genotypes, with FH1/FH1 having a significant lower mean LDL-C level at baseline (p=0.04), and a greater reduction in LDL-C following 3 months of ezetimibe therapy compared to FH1/FH2 (-17.5% vs -11.5%, p=0.027). Lastly, there was no significant difference in LDL-C at baseline or 3 months between gender. However females tended to show a slightly better mean percentage

reduction at 3 months (-20.7% vs -17%; p = 0.49).When patients were divided into those who responded to ezetimibe (mean percentage reduction of > 20%), compared to those with that did not (mean percentage reduction of < 20%), no identifiable factor such as BMI, gender or FH genotype was shown to be significant in identifying those patients who were more likely to respond.

Conclusion: Ezetimibe is effective in HoFH and, on top of statin therapy, can reduce LDL-C by a further 18.9%. Ezetimibe should therefore be considered in all HoFH patients in order to lower LDL-C levels further. BMI and FH genotype influenced the response to ezetimibe. However, no single factor was able to predict response in the individual patient.

DECLARATION

I, Dr Adriano Dello Iacono declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the Department of Internal Medicine, Faculty of Health Sciences, at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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DEDICATION

To my supervisor, Professor Frederick Raal, whose guidance, wisdom and expertise were always available. He has been a role model for me throughout my under and post-graduate studies

To my amazing girlfriend, Samantha Lake, for her love, understanding, motivation and inspiration.

To my parents Antonio and Antoinette Dello Iacono for their constant support, love and encouragement.

To my Sister Francesca Burger and brother in law Josh Burger, for their guidance and motivation.

To all other members of my family and friends not mentioned above, for their support, love and encouragement.

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ABBREVIATIONS

APOB	Apolipoprotein B
APOC2	Apolipoprotein C2
APOE	Apolipoprotein E
BMI	Body Mass Index
CAD	Coronary artery disease
CE	Cholesteryl Esters
CI	Confidence Intervals
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
FFA	Free fatty Acids
FH	Familial Hypercholesterolaemia
FH1	Afrikaner 1 mutation
FH2	Afrikaner 2 mutation
FH3	Afrikaner 3 mutation
HDL-C	High Density Lipoprotein-cholesterol
HeFH	Heterozygous Familial Hypercholesterolaemia
HMG-COA	Hydroxymethylglutaryl Co-enzyme A
HoFH	Homozygous Familial Hypercholesterolaemia
IHD	Ischaemic Heart Disease
LCAT	Lecithin Cholesterol Acyltransferase
LDL-C	Low Density Lipoprotein-cholesterol
LDL	Low Density Lipoprotein
LDLR	Low Density Lipoprotein Receptor
LDLRAP1	Low Density Lipoprotein Receptor Adapter Protein 1
LPL	Lipoprotein Lipase
mRNA	Messenger Ribonucleic acid
MTP	Microsomal triglyceride transfer protein
NPC1L1	Niemann Pick C1 Like 1
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PLTP	Phospholipid transfer protein
RCT	Reverse Cholesterol Transport
SD	Standard Deviation
SR-B1	Scavenger Receptor B1
SREBP	Sterol Regulatory Element Binding Protein
TG	Triglycerides
TIA	Transient Ischaemic Attack
VLDL	Very Low Density Lipoprotein